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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32721A/USN	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11271	International filing date *(day/month/year)* 10.10.2003	Priority date *(day/month/year)* 11.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/44		
Applicant NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2004	01.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Beranová, P Telephone No. +49 30 25901-333

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11271

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-9 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 11

   because:

   ☒ the said international application, or the said claims Nos. 11 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6
	No:	Claims	1-3,7-12
Inventive step (IS)	Yes:	Claims	5,6
	No:	Claims	1-4,7-12
Industrial applicability (IA)	Yes:	Claims	1-10,12
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3.1 Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 Reference is made to the following documents:

D1: FAGIN J A: "Perspective: Lessons learned from molecular genetic studies of thyroid cancer: Insights into pathogenesis and tumor-specific therapeutic targets" ENDOCRINOLOGY, BALTIMORE, MD, US, vol. 143, no. 6, June 2002 (2002-06), pages 2025-2028, XP002251224 ISSN: 0013-7227

D2: LEVITZKI A: "Tyrosine kinases as targets for cancer therapy" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, September 2002 (2002-09), pages S11-S18, XP004402495 ISSN: 0959-8049

D3: SELLE B ET AL: "ABL-specific tyrosine kinase inhibitor imatinib as salvage therapy in a child with Philadelphia chromosome-positive acute mixed lineage leukemia (AMLL)" LEUKEMIA (BASINGSTOKE), vol. 16, no. 7, July 2002 (2002-07), pages 1393-1395, XP002268892 ISSN: 0887-6924

D4: CAPDEVILLE R ET AL: "Imatinib: the first 3 years" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, September 2002 (2002-09), pages S77-S82, XP004402504 ISSN: 0959-8049

D5: KANO Y ET AL: "IN VITRO CYTOTOXIC EFFECTS OF A TYROSINE KINASE INHIBITOR STI571 IN COMBINATION WITH COMMONLY USED ANTILEUKEMIC AGENTS" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 97, no. 7, 1 April 2001 (2001-04-01), pages 1999-2007, XP001035243 ISSN: 0006-4971

D6: TOPALY J ET AL: "SYNERGISTIC ACTIVITY OF STI571 WITH CHEMOTHERAPEUTIC DRUGS AND IRRADIATION" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 96, no. 11, PART 1, 1 December 2000 (2000-12-01), page 736A, XP009010656 ISSN: 0006-4971

D7: EP-A-0 564 409 (CIBA GEIGY AG) 6 October 1993 (1993-10-06)
D8: US-A-5 521 184 (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28)

5.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 3 and 7 - 12 is not new in the sense of Article 33(2) PCT.

The document **D1** reports the use of imatinib mesylate for the treatment of chronic myelogenic leukemia (page 2026, right-hand column, 2nd paragraph). This document is therefore considered to be relevant for novelty of the subject-matter of claims 1, 10 and 11.

D2 shows a successful use of STI 571 (imatinib mesylate) for the treatment of chronic myelogenic leukemia and gastrointestinal stromal tumors (page S14, right-hand column; page S15, Figure 3). D2 thus takes away novelty of claims 1, 2, 10 and 11.

D3 teaches about a successful treatment of acute leukemia with imatinib (page 1394, right-hand column, last paragraph). It is therefore novelty-destroying for claims 1, 2, 11 and 12.

D4 shows that imatinib mesylate (Gleevec, STI 571) is effective in the treatment of chronic myeloid leukemia, caused by enhanced expression of Bcr-Abl and reports synergistic interactions of imatinib with various chemotherapeutic agents incl. mitoxantrone and topotecan in leukemic cells (page S79, right-hand column, 2nd paragraph; page S80, left-hand column, 2nd paragraph). D4 is thus relevant for novelty of claims 1, 2 and 7 - 11.

D5 mentions that imatinib mesylate (STI 571) produced additive effects with doxorubicine in chronic myelogenous leukemia cells and in acute myoblastic leukemia cells. Furthermore, it suggests that simultaneous administration of STI 571 with other agents would be advantageous (page 1999, abstract). This document is therefore considered to be relevant for novelty of the subject-matter of claims 1, 2 and 7 - 12.

D6 shows that imatinib mesylate and mitoxantrone exhibit a synergistic effect on inhibition of the proliferation of BCR-ABL+ leukemic cells (abstract). In view of this document, no novelty exists for claims 1 - 3 and 7 - 11.

5.3 Should the applicant overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated over D1 - D6, as the present subject-matter of claims 1 - 3 and 7 - 12, as far as novel, appears to be obvious over said documents (Article 33(3) PCT).

5.4 Claims 4 - 6 are considered as formally novel. However, it is pointed out that claim 4 lacks inventive step, the reasons being as follows:

The problem to be solved by the present application may be regarded as reversion of resistance to anti-cancer agents.

However, the solution to this problem is disclosed in the document D7 which mentions that imatinib derivatives are able to avoid occurrence of resistance to chemotherapeutic drugs and to reverse existing resistance in the treatment of cancer (page 5, lines 36 - 38). Additionally, D8 discloses imatinib derivatives with anti-tumor activity which are able to prevent the development of resistance in cancer treatment with other chemotherapeutic agents or remove existing resistance (column 7, lines 44 - 45; column 8, lines 6 - 7; column 9, lines 1 - 4). The skilled person would therefore regard the use of imatinib (and its derivatives) as an obvious option in order to solve the problem posed.

5.5 For the assessment of the present claim 11 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.6 It is pointed out that second medical use claims 3 - 6 are not acceptable under Article 6 PCT. The therapeutic application is functionally defined by a mechanism of action (**"inhibiting breast cancer resistance protein", "to prevent or reverse resistance to an anticancer agent", "improving the absorption of an orally administered anticancer agent"**) which does not allow any practical application in form of a defined, real treatment of a pathological condition or disease.